

FILE 'MEDLINE' ENTERED AT 19:45:21 ON 04 JUN 1997

L1 370 S B7-2
L2 2681 S TH2 OR T HELPER 2
L3 6637 S IL-4
L4 519449 S STIMUL####
L5 212 S L1 AND (L2 OR L3 OR L4)
L6 265761 S SKEW### OR DIFFERENTIAL OR BIAS
L7 18 S L5 AND L6
L8 194 S L5 NOT L7
L9 19 S L8 NOT PY>1994
L10 69 S L1 AND CYTOKINE
L11 106 S L1 AND CYTOKINE#
L12 8 S L11 NOT PY>1994
L13 5137 S STIMULAT### (2A) T CELL#
L14 1338 S STIMULAT### (2A) T LYMPHOCYTE#
L15 6304 S L13 OR L14
L16 7 S L1 (6A) L15
L17 75 S L1 AND L15
L18 4 S L17 NOT PY>1994

L15 ANSWER 1 OF 10 MEDLINE

AN 97211831 MEDLINE

TI Human T helper cell differentiation is regulated by the combined action of cytokines and accessory cell-dependent costimulatory signals.

AU Palmer E M; van Seventer G A

CS Department of Pathology, University of Chicago, IL 60637, USA.

NC AI34541 (NIAID)

AI7090 (NIAID)

SO JOURNAL OF IMMUNOLOGY, (1997 Mar 15) 158 (6) 2654-62.

Journal code: IFB. ISSN: 0022-1767.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 9706

EW 19970601

AB We have developed an in vitro differentiation model for human Th cells to study the role of cytokines and accessory cell-dependent costimulatory signals in this process. Peripheral blood-derived CD4+ "naive" (CD45RA+ RO-) T cells were **stimulated** in weekly intervals with immobilized anti-CD3 mAb, accessory cells, and exogenous cytokines, and were analyzed for cytokine secretion pattern. With the B cell line JY (B7-1+ B7-2+), as source of accessory cells, we could generate distinct Th subsets. Coculture with the combination of recombinant human (rh) IL-1beta and rhIL-6 gave rise to Th0-like cells, which secreted low levels of IFN-gamma and IL-5. The addition of rhIL-12 led to the generation of Th1-like cells, which secreted high levels of IL-2, IFN-gamma, TNF-alpha, and upon multiple stimulations, significant levels of IL-10. The presence of rhIL-4 induced **Th2**-like cells that secreted high levels of IL-5 and IL-13, but undetectable levels of IL-4. Only after **stimulation** with phorbol ester and calcium ionophore could these **Th2**-like cells be induced to secrete significant levels of IL-4, indicating distinct **stimulatory** requirements for the induction of IL-5 and IL-13 compared with IL-4. The B7-1-negative monocytic cell line U937 could only provide accessory cell-dependent costimulatory signals for the generation of Th1-like cells, while B7-1-transfected U937 cells acquired the capacity to provide costimulation for the generation of **Th2**-like cells. These results indicate a differential dependence on **CD28**-mediated costimulation for the generation of human Th1-like and **Th2**-like cells.

L15 ANSWER 2 OF 10 MEDLINE

AN 97163972 MEDLINE

TI CD80, CD86 and CD40 provide accessory signals in a multiple-step T-cell activation model.

AU Van Gool S W; Vandenberghe P; de Boer M; Ceuppens J L

CS Department of Pathophysiology, Catholic University of Leuven, Belgium.

SO IMMUNOLOGICAL REVIEWS, (1996 Oct) 153 47-83. Ref: 150

Journal code: GG4. ISSN: 0105-2896.

CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 9706
EW 19970602
AB In this review, a sequential multiple-step model for T-cell activation is proposed. In a series of in vitro studies, highly purified freshly isolated human peripheral blood T lymphocytes were **stimulated** through the **CD28** receptor, with mAb or with natural ligands B7-1 or **B7-2**, along with TCR **stimulation**, in the absence of other costimulatory interactions. Ligation of the **CD28** receptor, along with **stimulation** of the TCR, was found to up-regulate pleiotropic in vitro activities, including the secretion of both Th1 and Th2-type cytokines, B-cell help, and the development of cytotoxic activity. This costimulatory action involves CD4+ and CD8+ as well as naive and memory T-cell subsets. The expression of B7-1 and **B7-2** on professional APC in situ in both normal and pathological tissues, and its up-regulation on monocytes by GM-CSF and IFN-gamma is consistent with this role. Additional studies have addressed the contribution of interactions between **CD28** and B7-1 and **B7-2** in T-cell activation initiated by normal un-engineered APC, such as **stimulation** with recall antigens and primary MLR. Blockade of the interaction between **CD28** and B7-1/**B7-2** under these conditions failed to completely inhibit T-cell responses or to induce anergy. Complete inhibition and anergy were, however, induced with a combination of CsA, targeting downstream TCR-triggered signalling, as well as anti-B7-1- and anti-**B7-2**-directed reagents. Interestingly, and in contrast to anti-LFA-1 mAb, the addition of anti-B7-1 or anti-**B7-2** reagents could be delayed until at least 48 h after the initiation of T-cell **stimulation**, indicating a requirement for a late interaction between **CD28** and its counter-receptors. Interactions between CD40L on activated T cells and CD40 on APC may serve to sustain, enhance or prolong the presentation of B7-1 or **B7-2** on the APC, and thus to prevent anergy induction, or ineffective or abortive T-cell **stimulation**. Based on these data a sequential multiple-step T-cell activation model is proposed, and novel strategies for immuno-intervention can be designed.

L15 ANSWER 3 OF 10 MEDLINE
AN 97098504 MEDLINE
TI Costimulatory function and expression of CD40 ligand, CD80, and CD86 in vascularized murine cardiac allograft rejection.
AU Hancock W W; Sayegh M H; Zheng X G; Peach R; Linsley P S; Turka L A
CS Department of Pathology, New England Deaconess Hospital, Boston, MA 02215, USA.
NC AI-37691 (NIAID)
AI-34965 (NIAID)
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Nov 26) 93 (24) 13967-72.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)

LA English
 FS Priority Journals; Cancer Journals
 EM 9703
 EW 19970303
 AB Recent data implicates a role for the CD40-CD40 ligand (CD40L) pathway in graft rejection. One potential mechanism is direct costimulation of T cells through CD40L. Alternatively, the ability of CD40 **stimulation** to induce CD80 (B7-1) and CD86 (B7-2) expression on antigen-presenting cells (APCs) has led to the hypothesis that the role of CD40-CD40L interactions in transplant rejection might be indirect, i.e., to promote the costimulatory capacity of APCs. Here, we have used a murine vascularized cardiac allograft model to test this hypothesis. Treatment of the recipients with donor splenocytes and a single dose of anti-CD40L mAb induces long-term graft survival (> 100 days) in all animals. This is associated with marked inhibition of intragraft Th1 cytokine [interferon gamma and interleukin (IL) 2] and IL-12 expression with reciprocal up-regulation of Th2 cytokines (IL-4 and IL-10). In untreated allograft recipients, CD86 is strongly expressed on endothelial cells and infiltrating mononuclear cells of the graft within 24 hr. In contrast, CD80 expression is not seen until 72 hr after engraftment. Anti-CD40L mAb has no detectable effect on CD86 up-regulation, but almost completely abolishes induction of CD80. However, animals treated with anti-CD80 mAb or with a mutated form of CTLA4Ig (which does not bind to CD86) rejected their cardiac allografts, indicating that blockade of CD80 alone does not mediate the graft-prolonging effects of anti-CD40L mAb. These data support the notion that the role of CD40-CD40L in transplant rejection is not solely to promote CD80 or CD86 expression, but rather that this pathway can directly and independently costimulate T cells. These data also suggest that long-term graft survival can be achieved without blockade of either T cell receptor-mediated signals or **CD28**-CD86 engagement.

L15 ANSWER 4 OF 10 MEDLINE
 AN 97079723 MEDLINE
 TI **B7-2** (CD86) is essential for the development of IL-4-producing T cells.
 AU Ranger A M; Das M P; Kuchroo V K; Glimcher L H
 CS Department of Cancer Biology, Harvard School of Public Health, Boston, MA 02115, USA.
 SO INTERNATIONAL IMMUNOLOGY, (1996 Oct) 8 (10) 1549-60.
 Journal code: AY5. ISSN: 0953-8178.
 CY ENGLAND: United Kingdom
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 9704
 EW 19970403
 AB The **CD28**/CTLA-4 ligands, B7-1 (CD80) and **B7-2** (CD86), provide a co-**stimulatory** signal necessary for optimal T cell activation. We have examined the effect of blocking B7-1 and **B7-2** in an in vitro system using ovalbumin-specific T cells from alpha beta TCR-transgenic mice. This system allowed us to examine the interaction of B7 co-**stimulators** on physiologic antigen-presenting cells (APC) with antigen-specific T helper precursor (ThP) cells. We report that blocking Thp/B7-1 or **B7-2** interactions in a primary response differentially affects the cytokine profile

observed in a secondary **stimulation**, even in the absence of additional anti-B7 antibody. Engagement of **B7-2** in the primary **stimulation** was found to be essential for production of the **Th2** cytokine, IL-4, but not the Th1 cytokines, IL-2 and IFN-gamma, in a secondary **stimulation**. Conversely, inclusion of the anti-B7-1 mAb in cultures using highly purified naive T cells increased levels of IL-4 and significantly depressed levels of IFN-gamma, upon re-**stimulation**. The effect of the anti-**B7-2** mAb in reducing IL-4 production could be overcome by the addition of recombinant IL-4 in the primary **stimulation**. The effects of the anti-**B7-2** mAb appear to be due to blocking and not cross-linking, as F(ab) fragments mimicked the intact antibody. Taken together, our data demonstrate that the interaction between Thp and **B7-2** favors the development of **Th2** cells.

L15 ANSWER 5 OF 10 MEDLINE

AN 96286034 MEDLINE

TI Differential effect of the immunomodulator AS101 on B7-1 and **B7-2** costimulatory molecules: role in the antitumoral effects of AS101.

AU Kalechman Y; Sredni B

CS Cancer, AIDS, Immunology Research, (CAIR), Department of Life Sciences, Bar Ilan University, Ramat Gan, Israel.

SO JOURNAL OF IMMUNOLOGY, (1996 Jul 15) 157 (2) 589-97.
Journal code: IFB. ISSN: 0022-1767.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 9701

EW 19970104

AB The **CD28** receptor on T cells with its ligand B7, representing the best characterized example of costimulation, has recently been demonstrated to interact with two different ligands: B7-1 and **B7-2**. AS101 (ammonium trichloro[dioxoethylene-O,O']tellurate), a synthetic immunomodulator with minimal toxicity, was previously shown to **stimulate** both mouse and human cells to proliferate and secrete a variety of cytokines. We recently found that treatment of advanced cancer patients or tumor-bearing mice with AS101 results in a clear predominance of Th1 responses with a concomitant decrease in **Th2** response. Our present study demonstrates that AS101 differentially affects B7-1 and **B7-2** molecule expression on mouse macrophages: it up-regulates B7-1 expression in a dose-dependent manner without affecting **B7-2** expression, which leads to a profound macrophage costimulatory activity of purified T cells with soluble anti-CD3. Our results also demonstrate the differential inhibitory effect of IL-10 on T cell activation in the presence of AS101-**stimulated** accessory cells (AC). We show that when **stimulated** with AS101, AC-dependent T cell activation was more resistant to inhibition by IL-10 compared with AC **stimulated** by LPS. This was due to the partial resistance of AS101-**stimulated** macrophages to the down-regulation of B7-1 expression by IL-10. In vivo studies with AS101-treated tumor-bearing mice revealed that the predominance in Th1 responses--marked by an increase in IFN-gamma and a decrease in IL-4--may be associated in part with the ability of AS101 to

up-regulate B7-1 expression, which is also related to its antitumoral effects. These results suggest that AS101 may be clinically effective in conditions involving dysfunctional cytokine production.

L15 ANSWER 6 OF 10 MEDLINE

AN 96247623 MEDLINE

TI TCR-independent activation of human CD4+ 45RO- T cells by anti-**CD28** plus IL-2: Induction of clonal expansion and priming for a **Th2** phenotype.

AU Brinkmann V; Kinzel B; Kristofic C

CS Department of Asthma and Allergy Research, Pharmaceuticals Division, Ciba-Geigy Limited, Basel, Switzerland.

SO JOURNAL OF IMMUNOLOGY, (1996 Jun 1) 156 (11) 4100-6.

Journal code: IFB. ISSN: 0022-1767.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 9610

AB In this study we show that uncommitted human CD4+ CD45RA+ RO- CD25- CD71- HLA-DR- T cells can be primed for a **Th2** phenotype before they encounter TCR signals and before they are exposed to IL-4. We found that >99% of uncommitted T cells proliferated upon costimulation by immobilized anti-CD3 plus anti-**CD28** mAbs and differentiated into pure Th1 cells. In contrast, uncommitted T cells did not respond to **stimulation** by either anti-CD3 or anti-**CD28**, or by IL-2 alone. Interestingly, 5% of uncommitted T cells proliferated efficiently in response to **stimulation** by immobilized anti-**CD28** plus IL-2 (in the absence of TCR/CD3 signals) and differentiated into pure **Th2** "precursor" cells. Like murine CD4+ NK1.1+ T cells, human **Th2** precursors promptly expressed mRNA for **Th2** cytokines upon **stimulation** via the TCR/CD3 complex by anti-CD3 mAb or staphylococcal enterotoxin B, and secreted up to 50 ng of IL-4, IL-5, and IL-13 per 10(6) cells. **Th2** "precursors" developed only in the complete absence of IL-4, as addition of 0.1 U (5 pg) of exogenous IL-4 suppressed their clonal expansion by >90%, whereas addition of neutralizing anti-IL-4 mAb had no effect. Together these results suggest that, in vivo, a significant fraction of uncommitted T cells may be primed for a **Th2** phenotype independent of Ag and IL-4 if they are exposed to Th1 cell-derived IL-2 and simultaneously interact with accessory cells bearing the natural **CD28** ligands B7-1 and **B7**-2. When **stimulated** by specific Ag, such primed **Th2** precursor cells may provide a source of IL-4 to promote **Th2** immunity.

L15 ANSWER 7 OF 10 MEDLINE

AN 96182297 MEDLINE

TI Interferon-gamma and interleukin-10 inhibit antigen presentation by Langerhans cells for T helper type 1 cells by suppressing their CD80 (B7-1) expression.

AU Ozawa H; Aiba S; Nakagawa; Tagami H

CS Department of Dermatology, Tohoku University School of Medicine, Sendai, Japan.

SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1996 Mar) 26 (3) 648-52.

Journal code: EN5. ISSN: 0014-2980.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 9607
 AB CD80(B7-1) and CD86(B7-2) co-stimulatory molecules have been reported to activate Th1/Th2 development pathways differentially. It is well known that Langerhans cells (LC), potent antigen-presenting dendritic cells in the epidermis, express several co-stimulatory molecules and that this expression is modulated by several cytokines. Based on the recently reported effect of interferon (IFN)-gamma and interleukin (IL-)-10 on the expression of CD80 and CD86 by LC, we examined the effects of these cytokines on the expression of CD54 (intercellular adhesion molecule-1) and CD40 in addition to CD80 and CD86 on LC, and correlated the expression of each co-stimulatory molecule with antigen presentation for a Th1 clone by cultured LC (cLC) treated with these cytokines. LC cultured for 72 h significantly up-regulated MHC class II antigen expression and all the co-stimulatory molecules were examined. As previously reported, IL-10 or IFN-gamma inhibited the up-regulation of CD80 expression. Granulocyte/macrophage-colony-stimulating factor (GM-CSF) partially restored the suppression of CD80 expression induced by IFN-gamma on cultured LC, while it had virtually no effect on the inhibition induced by IL-10. Antigen presentation for the myoglobin-specific syngeneic Th1 clone by cLC, which were pre-incubated with these cytokines, correlated well with their CD80 expression. In addition, among the antibodies for CD80, CD86, CD28 or CD40, the suppression of the Th1 clone stimulation by LC was found to occur only with anti-CD80 and anti-CD28 antibodies. Finally, we studied the effects of IFN-gamma and IL-10 on GM-CSF production by epidermal keratinocytes (KC). We could show that only IFN-gamma, but not IL-10, suppressed GM-CSF production by KC. These findings suggest that both IFN-gamma and IL-10 suppress antigen presentation by LC for Th1 cells by suppressing their CD80 expression. The inhibitory effect of IFN-gamma on CD80 expression on LC appears to be partially mediated through the suppression of GM-CSF production by KC.

L15 ANSWER 8 OF 10 MEDLINE

AN 96152721 MEDLINE

TI Comparison of CD28-B7.1 and B7.2 functional interaction in resting human T cells: phosphatidylinositol 3-kinase association to CD28 and cytokine production.

AU Ghiotto-Ragueneau M; Battifora M; Truneh A; Waterfield M D; Olive D

CS INSERM U119, Marseille, France.

SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1996 Jan) 26 (1) 34-41.

Journal code: EN5. ISSN: 0014-2980.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 9605

AB CD28 is a 44kDa homodimer present on T cells providing an important costimulatory signal for T cell proliferation, cytokine production and cytokine receptor expression. CD28 activation is mediated by interaction with its counter-receptors, B7.1/CD80 and B7.2/B70/CD86. The biochemical basis of these co-stimulatory signals are still poorly

understood, particularly in resting T cells. However, various biochemical pathways such as tyrosine phosphorylation, phospholipase C, sphingomyelinase and phosphatidylinositol 3-kinase (PI3-K) activation have been reported to play a role in **CD28** signaling in tumor T cell lines and **CD28**-transfected cells or pre-activated T cells. In addition, recent reports propose that **CD28**-B7.1 and **B7.2** interaction could be involved in the production of Th1 and Th2 cytokines, respectively, but the putative biochemical basis for these different functions is still unknown. We have analyzed the functional and molecular consequences of **CD28** activation by B7.1 and **B7.2** in human resting T cells. We demonstrate in this report that both **CD28**-B7.1 and **CD28**-**B7.2** interactions induce the association of PI3-K to **CD28** in the CD4 subpopulation, whereas it was barely detectable in CD8 cells. This association involves the binding of the src homology domain 2 (SH2) of p85 to tyrosine-phosphorylated **CD28** and does not require pre-activation by CD3-T cell receptor. Worthmannin, a specific inhibitor of PI3-K enzymatic activity within the nanomolar range also inhibits the interleukin-2 production induced by costimulation mediated by either the B7.1- and **B7.2**-transfected cells or **CD28** monoclonal antibodies. The only slight difference between B7.1 and **B7.2** costimulation is the IC50 of worthmannin being 25 and 110 nM, respectively, which could suggest differences in their activation of the T cell PI3-K.

L15 ANSWER 9 OF 10 MEDLINE

AN 96082355 MEDLINE

TI **CD28** ligands CD80 (B7-1) and CD86 (**B7-2**) induce long-term autocrine growth of CD4+ T cells and induce similar patterns of cytokine secretion in vitro.

AU Levine B L; Ueda Y; Craighead N; Huang M L; June C H

CS Immune Cell Biology Program, Naval Medical Research Institute, Bethesda, MD, USA..

SO INTERNATIONAL IMMUNOLOGY, (1995 Jun) 7 (6) 891-904.
Journal code: AY5. ISSN: 0953-8178.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 9602

AB The interaction of **CD28** and its ligands is critical for antigen-induced T cell activation. Recent studies have demonstrated the existence of at least two members of the B7 receptor family. In this report, the co-stimulatory signals provided by CD80 (B7-1) or CD86 (**B7-2**) were compared to **CD28** ligation by mAb. We demonstrate that the kinetics of induction of T cell proliferation after anti-CD3 stimulation was similar regardless of the form of co-stimulation. Similarly, B7-1 and **B7-2** could both maintain long-term expansion of CD4 cells. The co-stimulatory effects of both B7-1 and **B7-2** were dependent on **CD28** cross-linking, based on complete inhibition of proliferation by **CD28** antibody Fab fragments. Co-stimulation with B7-1 and **B7-2** induced high levels of cytokine secretion by resting T cells, and the effects of B7-1 and **B7-2** could not be distinguished. This conclusion is based on analysis of the initial

activation of **CD28**+ T cells, as well as T cell subpopulations consisting of CD4+ and CD8+ T cells. Both B7-1 and B7-2 could elicit IL-4 secretion from CD4+ T cells while anti-**CD28** antibody induced substantially less IL-4 secretion. Furthermore, both B7-1 and B7-2 could **stimulate** high levels of IFN-gamma and IL-4 from CD4+CD45RO+ cells, while neither B7 receptor could co-**stimulate** IFN-gamma and IL-4 secretion from CD4+CD45RA+ T cells. B7-1 and B7-2 could, however, co-**stimulate** CD4+CD45RA+ T cells to secrete IL-2. By contrast, when previously activated T cells were tested, re-**stimulation** of CD4+ T cell blasts with B7-1 or B7-2 resulted in higher secretion of IL-4 and IL-5 than anti-**CD28**, while re-**stimulation** with anti-**CD28** antibody maintained a higher level of secretion of IL-2 and IFN-gamma than B7-1 or B7-2. These observations may have important implications because they suggest that the manner of **CD28** ligation can be a critical determinant in the development of cytokine secretion that corresponds to Th1- and Th2-like patterns of differentiation. Together these observations suggest that there are no intrinsic differences between B7-1 and B7-2 in their ability to co-**stimulate** the populations of cells that we have tested.

L15 ANSWER 10 OF 10 MEDLINE
AN 94246159 MEDLINE
TI Keratinocyte-derived T cell costimulation induces preferential production of IL-2 and IL-4 but not IFN-gamma.
AU Goodman R E; Nestle F; Naidu Y M; Green J M; Thompson C B; Nickoloff B J; Turka L A
CS Department of Medicine, University of Michigan, Ann Arbor 48109..
NC 1P50AR41703 (NIAMS)
AR 38957 (NIAMS)
AR 40065 (NIAMS)
+
SO JOURNAL OF IMMUNOLOGY, (1994 Jun 1) 152 (11) 5189-98.
Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 9408
AB By using superantigens, we have found previously that keratinocytes activated by IFN-gamma could serve as accessory cells, providing costimulatory signals needed to induce T cell proliferation. Here, we compared the profile of cytokines produced by T cells **stimulated** in the presence of activated keratinocytes with the response seen using professional APCs. When keratinocytes are used as accessory cells there is a specific defect in T cell IFN-gamma production, whereas IL-2 and IL-4 are induced at levels comparable with those seen when professional APCs are used as accessory cells. Because keratinocytes express BB-1, a **CD28**-ligand distinct from B7-1 or B7-2 (which are found on professional APCs), we examined the possibility that the defect in IFN-gamma production might be a result of nonproductive **CD28** engagement. However, even when the **CD28** pathway is directly activated by a **stimulatory** mAb, there is no induction of IFN-gamma production in keratinocyte-supported cultures. In these same cultures IL-2 production is increased

10-fold, thus demonstrating a specific deficiency in the induction of IFN-gamma rather than a failure to respond to **CD28 stimulation**. Analysis by reverse transcriptase-PCR and ELISA for the inducible p40 chain of IL-12 reveals that keratinocytes produce little if any messenger RNA and no protein for IL-12 p40 compared with professional APCs. Addition of rIL-12 to keratinocyte-supported cultures restores IFN-gamma levels to those seen when professional APCs are present. Finally, when T cells are restimulated and analyzed at later time points (10 to 14 days) we find a refinement in cytokine profiles: T cells **stimulated** in the presence of professional APCs produced the Th1 cytokines IL-2 and IFN-gamma, whereas T cells **stimulated** in the presence of activated keratinocytes produced only the **Th2** cytokine IL-4. The specific ability of keratinocytes to induce a **Th2** response seems most closely linked to their absence of IL-12 production, and may be important in the maintenance of peripheral tolerance to self-Ags or in the immune response to exogenous Ags, pathogens, or haptens encountered in skin.

L19 ANSWER 1 OF 6 MEDLINE
 AN 97220139 MEDLINE
 TI CD8+ cells and not CD4+ T cells are hyporesponsive to CD28- and CD40L-mediated activation in HIV-infected subjects.
 AU Vingerhoets J; Kestens L; Penne G; De Vuyst H; Vandenbruaene M; Pelgrom Y; Bosmans E; de Boer M; Kasran A; Azuma M; Colebunders R; Ceuppens J L; Vanham G
 CS Laboratory of Immunology, Institute of Tropical Medicine, Antwerpen, Belgium.
 SO CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (1997 Mar) 107 (3) 440-7. Journal code: DD7. ISSN: 0009-9104.
 CY ENGLAND: United Kingdom
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 9706
 EW 19970602
 AB T cell dysfunction in HIV-infected subjects could be the consequence of altered sensitivity of CD4+ or CD8+ T cells to various costimulatory signals. Therefore, we studied proliferation and cytokine production in highly purified CD8+ and CD4+ T cells from HIV-infected and HIV- subjects, induced by co-activation via cell-bound CD80, **CD86** and CD40 or by allo-activation. Regardless of the nature of the first and the costimulatory signal, CD8+ T cells from patients proliferated consistently less than controls, while responses from CD4+ T cells were similar in patients and controls. This phenomenon was observed after ligation of CD28 combined with anti-CD3 or phorbol myristate acetate (PMA), but also after allogeneic **stimulation** and after activation by CD40 and anti-CD3. Anti-CD3 combined with CD80 or **CD86** induced a mixed Th1/Th2-type cytokine profile in both CD4+ and CD8+ T cells from controls, whereas anti-CD3 plus CD40 induced only low levels of Th2-type cytokines and no interferon-gamma (IFN-gamma) in CD4+ T cells. Compared with controls, CD4+ T cells from patients produced slightly lower levels of IL-10 but equal amounts of IFN-gamma, IL-4 and IL-5, while CD8+ T cells from patients produced less of all cytokines tested. In conclusion, responses of purified CD4+ T cells from HIV+ subjects to various costimulatory pathways are relatively intact, whereas CD8+ T cells are hyporesponsive at the level of proliferation and cytokine production. A generalized intrinsic CD8+ T cell failure might contribute to viral and neoplastic complications of HIV infection.

L19 ANSWER 2 OF 6 MEDLINE
 AN 97211838 MEDLINE
 TI Role of costimulators in T cell differentiation: studies using antigen-presenting cells lacking expression of CD80 or **CD86**.
 AU Schweitzer A N; Borriello F; Wong R C; Abbas A K; Sharpe A H
 CS Department of Pathology, Brigham & Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.
 NC P01AI35225 (NIAID)
 P01AI35297 (NIAID)

R01AI38310 (NIAID)

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SO JOURNAL OF IMMUNOLOGY, (1997 Mar 15) 158 (6) 2713-22.

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CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 9706

EW 19970601

AB For T cells to be optimally activated, recognition of Ag/MHC complexes by the TCR must be accompanied by a second, costimulatory signal that can be provided efficiently by the related costimulatory molecules CD80 (B7-1) and **CD86** (B7-2). Recently, CD80 and **CD86** have been implicated as differential determinants of Th1- vs Th2-type cytokine profiles. However, this remains a controversial issue since conflicting results have been obtained in different experimental models both in vivo and in vitro. To investigate the role of CD80 and **CD86** in Th subset differentiation, we have examined the cytokine profiles induced in TCR transgenic T cells **stimulated** by peptide in association with splenic APCs obtained from knockout mice that selectively lack expression of either the CD80 or the **CD86** molecule. Our data suggest that **CD86**, and to a lesser extent CD80, can make significant contributions to the production of both IL-4 and IFN-gamma. However, neither molecule plays an obligatory role in priming for the production of either effector cytokine. Furthermore, CD80 and **CD86** contribute to the magnitude of T cell activation, but do not appear to selectively regulate Th1 vs Th2 differentiation.

L12 ANSWER 5 OF 8 MEDLINE
AN 94321918 MEDLINE
TI Comparative analysis of B7-1 and **B7-2**
costimulatory ligands: expression and function.
AU Hathcock K S; Laszlo G; Pucillo C; Linsley P; Hodes R J
CS Experimental Immunology Branch, National Cancer Institute, National
Institutes of Health, Bethesda, Maryland 20892..
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Aug 1) 180 (2) 631-40.
Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9411
AB Antigen-specific T cell activation requires the engagement of the T
cell receptor (TCR) with antigen as well as the engagement of
appropriate costimulatory molecules. The most extensively
characterized pathway of costimulation has been that involving the
interaction of CD28 and CTLA4 on the T cell with B7 (now termed
B7-1) on antigen presenting cells. Recently, **B7-2**
a second costimulatory ligand for CTLA4, was described,
demonstrating the potential complexity of costimulatory
interactions. This report examines and compares the expression and
function of B7-1 and **B7-2**. Overall these results
indicate that (a) B7-1 and **B7-2** can be expressed
by multiple cell types, including B cells, T cells, macrophages, and
dendritic cells, all of which are therefore candidate populations
for delivering costimulatory signals mediated by these molecules;
(b) stimulating B cells with either LPS or anti-IgD-dextran induced
expression of both B7-1 and **B7-2**, and peak
expression of both costimulatory molecules occurred after 18-42 h of
culture. Expression of **B7-2** on these B cell
populations was significantly higher than expression of B7-1 at all
times assayed after stimulation; (c) blocking of **B7-**
2 costimulatory activity inhibited TCR-dependent T cell
proliferation and **cytokine** production, without affecting
early consequences of TCR signaling such as induction of CD69 or
interleukin 2 receptor alpha (IL-2R alpha); and (d) expression of
B7-1 and of **B7-2** can be regulated by a variety
of stimuli. Moreover, expression of B7-1 and **B7-2**
can be independently regulated by the same stimulus, providing an
additional complexity in the mechanisms available for regulating
costimulation and hence immune response.

L12 ANSWER 8 OF 8 MEDLINE
 AN 94123335 MEDLINE
 TI Signals and signs for lymphocyte responses.
 AU Janeway C A Jr; Bottomly K
 CS Section of Immunobiology, Yale University School of Medicine, New Haven, Connecticut 06510.
 NC AI-14579 (NIAID)
 AI-26810 (NIAID)
 CA-38350 (NCI)
 +
 SO CELL, (1994 Jan 28) 76 (2) 275-85. Ref: 88
 Journal code: CQ4. ISSN: 0092-8674.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, ACADEMIC)
 LA English
 FS Priority Journals; Cancer Journals
 EM 9405
 AB The adaptive immune response protects us from infection in a world of pathogens that is forever evolving new variants. As the system is built on the generation of an open repertoire of receptors, the recognition of self is unavoidable, and is guarded against by deletion during lymphocyte development of those cells that are specific for ubiquitous self antigens, and the silencing of those that are specific for self antigens only encountered after cells achieve functional maturity in the periphery. This silencing occurs when lymphocytes recognize antigens in the absence of suitable costimulatory molecules. By contrast, when the same cell encounters the same ligand on a cell that expresses costimulatory molecules, it will proliferate and differentiate into an effector cell. These effector cells mediate protective immunity when the antigen is carried by a pathogen, but they can mount autoimmune responses if the antigen is derived from self. The major costimulatory molecules for CD4 T cells appear to be B7 and **B7.2** that bind to the CD28 and CTLA-4 receptors on the T cell. The signals from the TCR appear to be integrated with those from the costimulator receptor, and the T cell response depends on the precise nature of these signals, further conditioned by **cytokines** present in the environment of the responding cell. B cells can be viewed in a similar way, with the costimulatory molecule CD40 ligand and **cytokines** coming mainly from CD4 helper T cells determining the fate of the responding B cell. The TCR is not simply an on and off switch, since the precise way in which the TCR is ligated determines the differentiation of the T cell and can alter the effector responses of established T cell lines. Thus, the response capabilities of T cells are more flexible than originally believed, and much of this flexibility comes from the interplay of TCR signals and signs from the environment. If the biochemical nature of these differential signaling pathways were known, it might be possible to develop simple pharmacological agents capable of diverting T cell responses from harmful to innocuous by getting the T cell to reinterpret the signals it is receiving via

its receptors. (ABSTRACT TRUNCATED AT 400 WORDS)

L29 ANSWER 25 OF 33 MEDLINE
 AN 95196263 MEDLINE
 TI B7-1 and B7-2 costimulatory molecules activate
 differentially the Th1/Th2 developmental pathways: application to
 autoimmune disease therapy.
 AU Kuchroo V K; Das M P; Brown J A; Ranger A M; Zamvil S S; Sobel R A;
 Weiner H L; Nabavi N; Glimcher L H
 CS Department of Neurology, Harvard Medical School, Boston,
 Massachusetts 02115.
 NC NS-30843 (NINDS)
 NS-26773 (NINDS)
 AI-21569 (NIAID)
 SO CELL, (1995 Mar 10) 80 (5) 707-18.
 Journal code: CQ4. ISSN: 0092-8674.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 9506
 AB CD4 T helper precursor cells mature along two alternative pathways,
 Th1 and Th2. Here we show that these pathways are differentially
 activated by two costimulatory molecules, B7-1 and B7-
 2. Using anti-B7 antibodies, this developmental step was
 manipulated both in vitro and in vivo in experimental
allergic encephalomyelitis (EAE). Anti-B7-1 reduced the
 incidence of disease while anti-B7-2 increased
 disease severity. Neither antibody affected overall T cell induction
 but rather altered cytokine profile. Administration of anti-B7-1 at
 immunization resulted in predominant generation of Th2 clones whose
 transfer both prevented induction of EAE and abrogated established
 disease. Since co-treatment with anti-IL-4
 antibody prevented disease amelioration, costimulatory molecules may
 directly affect initial cytokine secretion. Thus, interaction of
 B7-1 and B7-2 with shared counterreceptors CD28
 and CTLA-4 results in very different outcomes in clinical disease by
 influencing commitment of precursors to a Th1 or Th2 lineage.